Challenge TB - Transmission Project:
Quantifying effect of interventions on transmission of *Mycobacterium tuberculosis*

Year 1

Annual Report

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Cover photo: Workshop to develop protocol for core project transmission in Tanzania with local stakeholders, in Bagamoyo. June 2015 (Credit: Charles Mkubya).

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The authors' views expressed in this publication do not necessarily reflect the views of the United States Agency for International Development or the United States Government.

List of Abbreviations and Acronyms

ARTI	Annual Risk of Tuberculosis Infection
ATS	American Thoracic Society
CAR	Central Asia Region
CBO	Community Based Organization
CI	Confidence interval
CTB	Challenge TB
CTRL	Central TB reference laboratory
CXR	Chest X-Ray
DRS	Drug-Resistance Survey
DST	Drug sensitivity testing
EQA	External Quality Assurance
HCW	Health Care Worker
IGRA	Interferon Gamma Release Assays
IRB	Institutional Review Board
IRD	Interactive Research and Development
KNCV	KNCV Tuberculosis Foundation
MDR TB	Multi-drug resistant TB
MIRU	Mycobacterial Interspersed Repetitive Units
MoH	Ministry of Health
M.tb.	*Mycobacterium tuberculosis*
NIMR	National Institute for Medical Research (Tanzania)
NTLP	National TB and Leprosy control Programme
NTP	National TB control Programme
PI	Principal Investigator
PLHIV	People living with HIV
QFN	Quantiferon
RFLP	Restriction Fragment Length Polymorfism
SAB	Scientific Advisory Board
SOP	Standard Operating Procedure
TB	Tuberculosis
TB IC	TB infection control
TBD	To be determined
ToR	Terms of reference
TST	Tuberculin Skin Test
UCSF	University College of San Francisco
USAID	United States Agency for International Development
USD	US dollars
VNTR	Variable Number Tandem Repeat
WGS	Whole Genome Sequencing
WHO	World Health Organization

1. Executive Summary

Objectives
The overall objective of this Challenge TB (CTB) core project and overarching research question is: to evaluate to what extent United States Agency for International Development (USAID)-supported interventions have had an impact on transmission of *Mycobacterium tuberculosis (M. tb)*. We will investigate this in: a) specific facilities; b) among high-risk populations such as urban dwellers, miners, prisoners and; c) communities at large. The secondary objective is to map transmission patterns (both for TB and MDR-TB). Results of both objectives will provide recommendations for future USAID investments. Ultimately the findings of such studies will be used to develop/design and target future interventions. Exact study objectives and designs will be proposed in discussion with the countries where the study will take place. Interventions to be evaluated depend on planned CTB country activities. So far Tanzania and Indonesia have been selected, assessments will be carried out for possible inclusion to DR Congo, Nigeria, Kyrgyzstan, Zimbabwe and some others.

Management
USAID has asked American Thoracic Society (ATS) and KNCV Tuberculosis Foundation (KNCV) to lead this project. Management and support structures have been established, with USAID, KNCV and ATS being in the steering committee. On top of this, a charter and a Scientific Advisory Group of Experts (SAGE) was developed and approved in September 2015, comprising of CTB Coalition partners Interactive Research and Development (IRD), WHO, and other experts.

Activities
In February an expert consultation meeting took place in Washington DC with USAID staff, CTB partners (KNCV, ATS, WHO, FHI 360) and 12 other experts in the area of genotyping, community wide TB intervention studies and TB infection control. This consultation led to advice on priorities, site selection criteria and study designs. A work plan development workshop was held at KNCV with USAID, KNCV and ATS in April 2015. It was agreed to start with Indonesia and Tanzania, and KNCV will sub-contract in-country research partners to implement the studies.

After USAID/W approved the work plan in July 2015 and we received buy-in from the USAID Country Missions in 2 countries, a site assessment was done in Indonesia (September 2015), and in Tanzania a combined mission on site assessment and protocol development was held (September 2015).

Country progress: Tanzania
For Tanzania, a local research partner was proposed (the National Institute for Medical Research, NIMR) with which a sub-agreement is in development and a sole source waiver will be requested from the usual competitive bidding process, since NIMR is basically the only in-country partner that is able to perform such a task. An illustrative budget for four years was submitted.

Three sub-studies were proposed in Tanzania:

1. Does a package of interventions reduce transmission with rapid progression to active TB in the community? This study will include a whole (sub)-district;
2. Does the decentralization of treatment initiation of MDR-TB patients affect transmission of MDR-TB in Tanzania? This will be a country wide study;
3. Does screening of miners for active tuberculosis reduce transmission among miners and in their communities?

The first and main study was proposed being conducted in a sub-district of Kinondoni, part of Dar es Salaam region.[1] Both National TB and Leprosy Control Programme (NTLP) and NIMR welcomed the proposal and agreed with the choice of Kinondoni. In the meantime the USAID mission in Tanzania decided to change the Challenge TB regions, with Dar es Salaam no longer being a geographic focus area in CTB from mid-2016 onwards. As a result Kinondoni cannot be included in the project. At time of writing of this report 3 regions were announced as geographic focus areas for year 2, among which Kilimanjaro, Arusha and Iringa. Since a genotyping study was done before in Iringa, this region may be the best choice, since (a) the project can use infrastructure and staff that was build up in the previous project and (b) long term change in transmission (the previous study being considered a baseline) can be analyzed.

Country progress: Indonesia
In Indonesia the NTP and the local TB Operational Research Group (TORG) also welcomed the project. During the visit the strengths and weaknesses of 3 sites and potential implementing institutes were assessed by a set of predefined site criteria and criteria related to the laboratory. Based on these, a risk map was

[1] Kinondoni is a district in Dar es Salaam region for the national administration. Within the National TB and Leprosy Control Programme (NTLP) Kinondoni is a region, with 8 districts.

defined. The visits to the three research institutes, well prepared by each of them, showed a wide array of activities and capabilities. The conclusion is that for each site/partner combination there are one or more critical risks. The conclusions are that NTP leadership is in principle in support of the project, but will await recommendations by the TORG before final approval. The TORG is also in support (notwithstanding concerns about the size and ambition of the project) but recognizes that its feasibility will depend on where and by whom it will be implemented. It has been agreed to perform a competitive bidding process for local subcontracting based on a draft protocol.

Country progress: other countries
USAID encouraged the steering committee to expand on the number of countries (e.g. Kyrgyzstan, India, DRC, Nigeria) after which the committee proposed Zimbabwe as a possible alternative. A smaller protocol was developed on MDR-TB transmission for the Democratic Republic of the Congo (DRC), which may also be applied to Nigeria and/or Zimbabwe and Kyrgyzstan. This protocol was shared and welcomed by USAID/W.

For the three African countries site assessment information was collected and summarized and shared with USAID for discussion with USAID Country Missions whether a scoping mission could take place.

On the advice of USAID/W, further assessment of Kyrgyzstan was postponed due to administrative issues between Government of Kyrgyzstan and US government. Further assessment of India was postponed due to a possible link with an RFA on Urban TB. No decision was taken yet on a scoping mission to the other countries.

Year 2 outlook
In year 2 we expect to start data collection in Tanzania and Indonesia, and do scoping missions and protocol development in 3 other countries.

2. Introduction

Scientific rationale
The effects of USAID supported tuberculosis (TB) control interventions traditionally have been measured in terms of processes, outputs and impact on case detection and treatment success [TBCARE I M&E framework]. The impact of these interventions on reducing transmission of *Mycobacterium tuberculosis (M.tb),* the ultimate goal of control measures, is, however, unknown. To garner more precise information on the effect of prevention and care interventions, USAID intends to examine the impact of project interventions supported by USAID on transmission of *M.tb* at national or subnational levels. To assist in developing approaches in assessing *M.tb* transmission, USAID organized an expert consultation as part of Challenge TB Core Project*, Quantifying transmission of Mycobacterium tuberculosis transmission*, held on 4-5 February 2015 in Washington DC. This proposal is largely based on the discussions and recommendations of the expert consultation group, as well as subsequent discussions with USAID/W staff.

Measuring transmission
Measuring transmission of *M.tb* is challenging, since the transmission event itself cannot be observed. The result of transmission, infection with *M.tb*, is manifested either as Latent TB Infection (LTBI) or as active TB. LTBI can be detected indirectly only with a Tuberculin Skin Test (TST) or Interferon Gamma Release Assay (IGRA). Neither test can differentiate between recent infection and older infection. Repeated TSTs within specific periods of time would be required to identify a conversion from negative to positive as an indicator of recent TB infection for example. Moreover, progression to TB disease as a result of acquisition of infection is estimated to occur in only approximately 10% of those who are infected and can occur any time from a few weeks after infection to many years after infection has taken place. Among HIV infected persons this proportion of progression to TB disease after infection is much higher. In persons who develop active TB, substantial information about transmission sources, sites of transmission, risks for active disease, and overall control program performance can be generated by combining genotyping (molecular fingerprinting) of organisms isolated in the community with conventional epidemiological data. Given the differences between assessments of overall transmission and transmission resulting in active tuberculosis, the tests to be used and the study designs vary greatly depending on the questions being asked. However, the results of such studies can serve to identify and target specific interventions and then measure the effect.

TB in selected countries

Country selection was based on the selection criteria and recommendations from the expert consultation, the list of USAID focus countries, and discussions with USAID held in a teleconference on 10 June 2015. The expert consultation recommended studies should be located in two types of settings; 1) in Asia (low HIV, medium MDR-TB, large private sector) and 2) in Africa (high HIV, low MDR, small private sector), and possibly a third setting in central Asian region (CAR)/Eastern Europe with high MDR. The settings selected will be countries where the Challenge TB project is already involved.

After discussion with USAID the following countries are proposed:

1. Indonesia
2. Tanzania
3. Kyrgyzstan
4. India
5. DR Congo
6. Nigeria

Zimbabwe was added as possible alternative for Nigeria and/or DRC.

3. Progress by Objective/Sub-Objective

Specific for this Core project we have proposed to use indicators in line with CTB intervention area 5.3: "Measuring the effect of interventions on transmission". The following indicators were identified:

5.3.1 #/% of targeted population tested for TB infection through latent TB infection (LTBI) survey
5.3.2 #/% of HCW screened for TB infection
5.3.3 #/% of HCW screened for TB
5.3.4 #/% of TB patients in the study targeted area enrolled in the core transmission study
5.3.5 #/% of MDR-TB patients in a defined geographic area enrolled in the core transmission study

Since the studies have not started, the result for all these indicators is zero.

Our milestones for year 1 were:

1. **Expert consultation held in Washington, 4-5 February**
   The expert consultation was held in Washington with USAID staff, challenge TB partners (KNCV, ATS, WHO, FHI360) and 12 other experts in the area of genotyping, community-wide TB intervention studies and TB infection control. In total 27 experts met to discuss the set-up of this project. This led to advice on priorities, site selection criteria and study designs. Minutes were distributed.

2. **Work plan development workshop, 9-10 April at KNCV, the Hague**
   A work plan development workshop was held at KNCV with USAID, KNCV and ATS. It was agreed to start with Indonesia and Tanzania, and KNCV will sub-contract in-country research partners to implement the studies.

3. **Site assessments done in 2 countries and sites selected**
   After USAID had approved the workplan in July 2015 and got buy-in from the USAID Country Missions in 2 countries, a site assessment was done in Indonesia (September 2015). In Tanzania the project conducted a combined mission on site assessment and protocol development (September 2015).

   In Indonesia the NTP and local TB Operational Research Group (TORG) welcomed the project. During the visit the strengths and weaknesses of the 3 sites and potential implementing institutes were assessed by a set of predefined site criteria and criteria related to the laboratory. Based on these, a risk map was defined. The visits to the three research institutes, well prepared by each of them, showed a wide array of activities and capabilities. The conclusion is that for each site/partner combination there are one or more critical risks.
   The conclusions are that NTP leadership is in principle in support of the project, but will await recommendations by the TORG before final approval. The TORG is also in support (notwithstanding concerns about the size and ambition of the project) but recognizes that its feasibility will depend on where and by whom it will be implemented. It was agreed to perform a competitive bidding process for local subcontracting based on a draft protocol.

4. **Protocol developed, adapted to country situation**

   During the protocol development workshop in Tanzania three sub-studies were proposed:
   1. Does a package of interventions reduce transmission with rapid progression to active TB in the community? This study will include a whole (sub)-district;
   2. Does the decentralization of treatment initiation of MDR-TB patients affect transmission of MDR-TB in Tanzania? This will be a country wide study;
   3. Does screening of miners for active tuberculosis reduce transmission among miners and in their communities?

   The first and main study was proposed being conducted in a sub-district of Kinondoni, part of Dar es Salaam region[2]. Both National TB and Leprosy Control Programme (NTLP) and NIMR welcomed the proposal and agreed with the choice of Kinondoni. In the meantime USAID mission has decided to change the Challenge TB regions, and Dar es Salaam will no longer be in CTB from mid-2016 onwards. As a result Kinondoni cannot be included in the project. At time of writing of this report 3 regions were announced for year 2, among which Kilimanjaro, Arusha and Iringa. Since a genotyping study was done before in Iringa, this region may be the best choice, since (a) the project can use infrastructure and staff that was build up in the previous project and (b) long term change in transmission (the previous study being considered a baseline) can be analyzed.

   For Indonesia the study protocol could not yet been developed awaiting the results of a tender process to select the local partner institutions.

5. **Strategic advisory board and other management/support structures established**
   USAID has requested ATS and KNCV to lead this project. Management and support structures have been established, with USAID, KNCV and ATS being in the steering committee. A charter and member list for a scientific advisory group of experts (SAGE) was developed and approved in September. Members including those from WHO and IRD, are invited for a first meeting on 1 December during the Union conference in Cape Town.
6. **Administrative permissions obtained in countries**
   Verbal agreement was obtained from NTP and USAID missions in Indonesia and Tanzania. In Indonesia verbal agreement was also obtained from the TB operational Research Group (TORG) and in Tanzania

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from the district authorities in the selected district (Kindondoni district in Dar es Salaam). We expect written agreements when protocols are fully finalized and approved.

7. **Subcontracting in place with local research partner**
   For Tanzania, a local research partner was proposed (the National Institute for Medical Research, NIMR) with which a sub-agreement is in development and a sole source waiver will be requested from the usual competitive bidding process, since NIMR is basically the only in-country partner that is able to perform such a task. An illustrative budget for four years was submitted.

8. **Investigations done on option to add Kyrgyzstan and 2/3 other countries**
   USAID encouraged the steering committee to expand the number of countries. A smaller protocol was developed on MDR transmission for DR Congo, which may also be applied to Nigeria and/or Zimbabwe and Kyrgyzstan. This protocol was shared and welcomed by USAID/W. For the three African countries site assessment information was collected and summarized and shared with USAID for discussing with US country missions whether a scoping mission could be performed.

   On the advice of USAID/W, an assessment of Kyrgyzstan was postponed due to administrative issues between the Government of Kyrgyzstan and US government. An assessment of India was postponed due to a possible link with an RFA on Urban TB.

4. Key Challenges during Implementation and Actions to Overcome Them

1. Short duration of the core project and delays in starting. Since TB is a slow epidemic, the effect of any intervention will take a long time to show a change in transmission. Since there are only 4 years left, and protocols still need to be finalized, we do not expect data collection to start before Q3 or Q4 of fiscal year 2. This leaves only 3 years for data collection, or 1 year before and 1 year after an intervention (which often takes a year to implement). We will partly overcome this by changing a before-after design into a trend analysis over 3 years.

2. Other delay factors:
   a. longer duration of approvals than expected for narrative, budget, and permissions from USAID Country missions to travel;
   b. time needed for waivers or tenders to select subcontractor and resource partners;
   c. USAID Country Mission in Tanzania decided to change CTB regions, resulting that our proposed region (Kinondoni), where all district and regional staff already agreed to the project, needs to change, causing another delay;
   d. Need for a 4 year illustrative budget in order to subcontract a local partner at a time when the detailed protocol is not ready.

   To mitigate these delaying factors we try to prepare documents and processes for new steps before previous steps are approved and closely monitor feedback.

3. In-country delays by NTLP in approvals of country visits. We overcome this by involving KNCV country office and using personal connections.

4. Time needed to keep a large number of stakeholders informed, involved and in agreement, for example in country: NTP, researcher partner, USAID/W, USAID Country Mission, KNCV country office, PMU, CTB partners, and within KNCV central office both technical focal persons and portfolio managers. We overcome this by wide distribution of visit reports and holding meetings and teleconferences. Maybe at some stage we should have a newsletter or website.

5. Low research capacity in some new countries. We will overcome this by involving experienced resource partners in those countries and local capacity building/training.

5. Lessons Learned/ Next Steps

Lessons learned

1. To measure impact from expected interventions on the transmission, we need to closely monitor implementation of these interventions. We will keep close track of timing of implementation processes, and the package of interventions already in place. Further we will budget additional activities to ensure high quality implementation of selected planned interventions to maximize effect on transmission.

2. The non-availability of high throughput Whole Genome Sequencing (WGS) capacity in projects countries requires the export of samples to an international lab. This seems possible even in countries where (local) researchers say it is difficult. ATS/UCSF has experience in genotyping and is currently requesting quotations and conditions from international high throughput WGS labs that have experience with M.*tb* samples. It is also budgeting for: sample transport abroad; training abroad of local lab staff to learn WGS; training abroad of a local statistician to learn bio-informatics.

3. The new way of organizing responsibilities and processes in CTB core projects related to CTB country offices needed some structuring. KNCV and ATS decided that all local partners will be subcontracted by the KNCV central office, even when ATS has technical lead. Some KNCV core project staff (funded from the core budget) will be placed at the KNCV/CTB country office to ensure smooth communication and coordination between central office and subcontractor. In countries where other CTB partners are lead partner, a feasible way of collaboration without duplication is still to be determined.

4. It takes much time to develop a solid justifiable budget for this amount of funding, in the context of still many unknowns, which meets USAID/W requirements.

5. Preparations in country take much time.

6. When this innovative project needs to expand to more than 2 countries, more time is needed from the scientific coordinator, portfolio manager/project coordinator and project officer.

Next steps

Within each country the following steps will take place:

- collect background info
- draft work plan
- obtain approval USAID/W & USAID Country Missions
- scoping mission (=site assessment) to select partners
- draft protocol
- sub-agreement development with local (or where necessary international) partner
- competitive bidding process/sole source waiver
- full protocol
- obtain USAID/SAGE approval

Subcontractor tasks with support from KNCV/ATS:

- ethics and admin permission
- develop data collection tools/SOP
- institute a local advisory board
- database development
- hiring of staff
- equipment buying
- training (int'l and local protocol specific)
- conduct pilot
- start data collection
- data collection & genotyping
- baseline cohort
- close cohort
- data analysis and reporting

Country specific steps:

- Tanzania: We will start with a new site visit and protocol development visit in November 2015. In the meantime a sub-agreement is in development and a waiver request is in preparation.
- Indonesia: we will start the tendering process for in country subcontractor in October 2015.
- 3 new countries: we will wait for assessment by USAID/W and permission of USAID Country Missions to have first scoping visits.
- Kyrgyzstan: await outcome of the elections.
- India: await guidance of USAID mission on RFA on urban TB.

Other general steps:

- Conduct first steering committee meeting and an annual meeting of the SAGE on 1 December in Cape Town.
- Discuss with USAID budget needs for the full 4 year work plan and per country budget.

Exact timings will be included in the work plan of year 2.